

Potential for Bias in Epidemiologic Studies That Rely on Glass-based Retrospective Assessment of Radon

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Retrospective assessment of exposure to radon remains the greatest challenge in epidemiologic efforts to assess lung cancer risk associated with residential exposure. An innovative technique based on measurement of α -emitting, long-lived daughters embedded by recoil into household glass may one day provide improved radon dosimetry. Particulate air pollution is known, however, to retard the plate-out of radon daughters. This would be expected to result in a differential effect on dosimetry, where the calibration curve relating the actual historical radon exposure to the remaining α -activity in the glass would be different in historically smoky and nonsmoky environments. The resulting "measurement confounding" can distort inferences about the effect of radon and can also produce spurious evidence for synergism between radon exposure and cigarette smoking. *Key words:* bias, cigarette smoking, confounding, dosimetry, epidemiologic methods, passive smoking, radon. *Environ Health Perspect* 103:1042–1046 (1995)

Radon is a noble gas formed as part of the radioactive decay chain of radium, which occurs naturally in the earth's crust. It seeps through the soil and accumulates in buildings, particularly if the structure has cracks beneath it and is tightly constructed to be energy efficient. Radon decays with a half-life of 3.8 days and forms radioactive lead, bismuth, and polonium "daughters" (Fig. 1) that can attach and emit α -radiation, penetrating the surfaces of the respiratory tract.

Data from underground miners who were occupationally exposed to high levels of radon show evidence of the carcinogenicity of radon (more precisely, of radon daughters) to the lung (1). The evidence for deleterious effects at the lower levels encountered in the typical home has been unconvincing (2–5), though such risk is highly plausible.

A number of case-control studies of residential radon exposure have been undertaken. The retrospective assessment of exposure requires the placement of long-term (usually year-long) radon measurement devices in each home in which the study participant has lived. The estimated house-specific exposures must then be combined, e.g., through integrating or averaging, for risk modeling. Such studies are highly labor intensive, and daunting practical difficulties arise. The residential histories provided by the study participant, including years of occupancy, must be verified, and the current occupant must agree to have detectors placed in the home. In some cases the house may not exist any more, the street may have been renamed or renumbered, or the house may have been structurally modified to the point where the relevance of the current radon levels to the levels formerly encountered by the study participant is dubious. There is also considerable room for mismea-

surement because of lifestyle differences; for example, the current occupant may sleep with a window open, whereas the study participant did not. Missing measurements, leading to large gaps in the reconstructed exposure histories are unavoidable, particularly in a residentially mobile population such as the United States. Experience in carrying out these difficult retrospective exposure assessments shows that radon measurements can be made for about 70% of study homes.

A recent breakthrough (6,7) could potentially both simplify and improve the retrospective assessment of residential radon exposure. The method makes use of glass objects that the study participant originally bought new and has taken from house to house over many years. If such objects can be identified, have been out in open display, and can be dated fairly precisely (e.g., a child's baby picture or a wedding picture), then the glass can provide an integrated measure of its exposure to radon daughters. Although appropriate glass objects are not always available, the feasibility of obtaining such measurements on household glass has been demonstrated (8) in the field in the context of a case-control study.

The short-lived radon daughters shown in Figure 1 are electrically charged and avidly form attachments to particles in the air and surfaces in the room. The attachment of these daughters to the room surfaces is called "deposition" or "plate-out." Once an α -emitting radionuclide, such as ^{218}Po or ^{214}Bi , has attached to the surface of a piece of glass in the room, the subsequent α decay produces an energetic enough "recoil" that (depending on the direction of emission of the α particle) the daughter product can become embedded a

short distance into the surface of the glass. The embedding is shallow, but deep enough to resist removal by usual cleaning methods (9).

Within a few weeks, virtually all the radon in a room will have decayed to ^{210}Pb , which has a very long half-life (22 years), but eventually decays to form (after a short incarnation as ^{210}Bi) ^{210}Po . A fraction of this ^{210}Po will have found its way, via plate-out followed by α -recoil embedding, into the surface of the glass. One can, in principle then, measure the α particles emitted by the embedded ^{210}Po , as a dosimetric marker for long-term radon daughter exposure. The presumption, for use of this technology in epidemiologic studies, is that the exposure of the glass can serve as a fairly good surrogate for the residential exposure of the study participant.

Figure 2 shows the fraction of radon that persists as ^{210}Po after varying lengths of time. This fraction was computed by applying exponential decay to the successive daughters in the decay chain shown in Figure 1, using the known half-lives for each species (see Appendix). If we make the simplifying assumption that the environmental conditions, including the patterns of ventilation and air turbulence, have remained approximately constant over the years, then this curve can be thought of as revealing the effective weighting function for the implicit integral over time captured by the measurement of ^{210}Po that remains embedded in the glass at time 0. Because of the long half-life of ^{210}Pb , the embedded ^{210}Po yields an integrated measure that effectively averages across decades, presumably reflecting exposures during the tenure of the glass in former residences as well as in the current residence. In this way, a piece of glass that was not previously owned and has been displayed by the study participant for 30 years can provide an integrated exposure measure over the decades of its ownership.

The empirical correspondence between the results of α -decay measurements based on household glass and measurements using long-term radon track-etch detectors has

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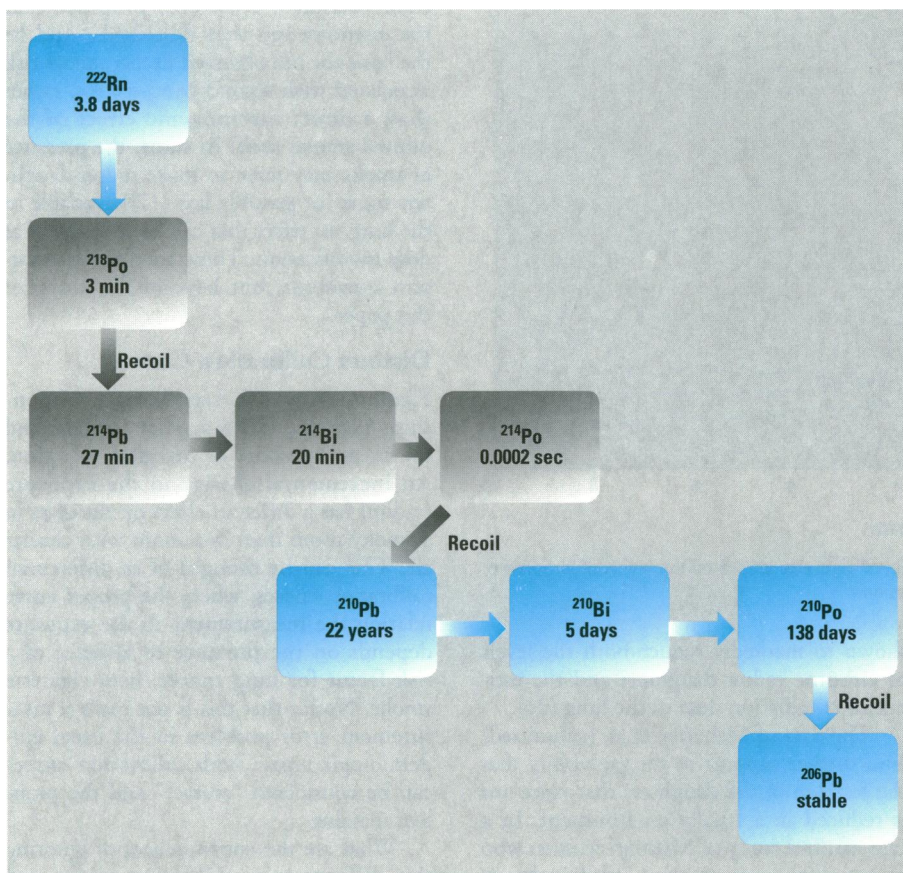


Figure 1. The predominant pathways in the decay of ^{222}Rn (radon) down to its stable descendant, ^{206}Pb . The vertical arrows correspond to α decays, which decrease the atomic weight by four, while the horizontal arrows correspond to β decays. The half-lives for each species are shown. The airborne carcinogenic descendants are shown by gray shading. Note that there are two points in the sequence where embedding via recoil into household glass can lead to embedded ^{210}Po : the decay of ^{218}Po already adhering to the glass to form ^{214}Pb and the decay of ^{214}Po already adhering to the glass to form ^{210}Pb .

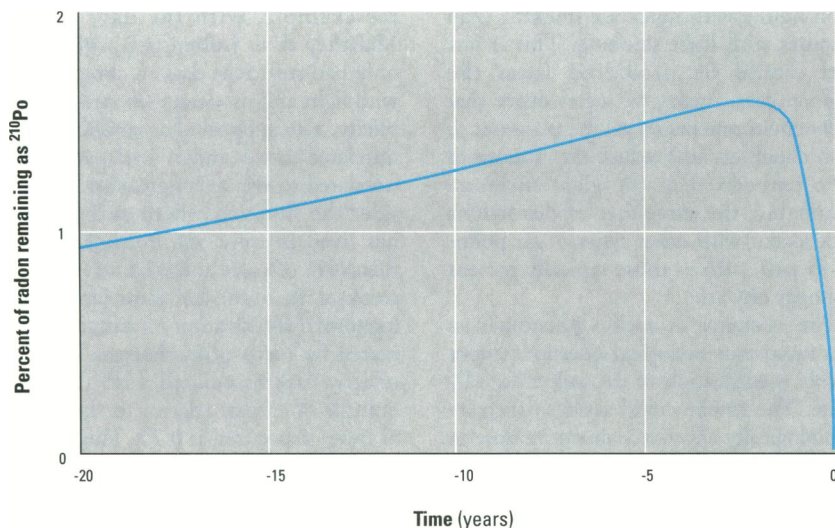


Figure 2. The fraction of radon daughter activity from that present at time t years remaining at time $t = 0$ in the form of ^{210}Po . For example, of the activity present in the room 20 years ago, almost 1% remains in the present time in the form of ^{210}Po .

been reasonably good (8–10). Methods recently developed now allow the measurement to be made without removing the glass from the home (8). The glass is cleaned, and a 2-inch square of CR-39 plastic is affixed to its surface and left in place for a few weeks. Next the plastic is removed, placed in a sealed bag, and mailed to the investigators, who count the alpha-tracks that have been etched into its surface by the ongoing random decay of ^{210}Po residing within the glass.

Although cigarette smoke contains radioactive ^{210}Po , this will not be embedded into the glass because the parent radionuclide is not in the smoke, and the smoke-based ^{210}Po therefore has no decay mechanism to cause it to embed in glass. Traces of this ^{210}Po that may remain in a film on the glass will be removed by cleaning, and this source is thought to contribute only negligibly to the measured α activity (11).

Plate-out

A key step in this process is the required initial attachment of the daughter radionuclides to the surface of the glass. Not all the radon daughters in a room plate-out. Many of these atoms remain airborne and are eventually vented out of the room as air circulates. The rate of plate-out depends on the aerosol content of the room air (12,13). If there are a lot of particles in the air, the radon daughters will tend to attach to the material in the air rather than to the surfaces, increasing the likelihood that they will ultimately be vented out of the room rather than attach to a surface.

An interesting set of experiments pertinent to this issue was conducted by Bergman and colleagues a decade ago (14). They took frequent (10/hr) measurements of the α radioactivity in the air of a room over 17 hr, beginning when the room ventilation system had just cycled off. After the levels had stabilized, they lit 12 cigarettes and let them burn passively in the room, giving off side-stream smoke into the ambient air. The results of one such series of experiments are shown in Figure 3. The figure shows the mean and high and low extremes of radioactivity for five control experiments with no cigarette smoke and corresponding results for studies with cigarette smoke. The levels of airborne radioactivity increase in the presence of smoke and remain elevated for hours. While there is, as noted above, some ^{210}Po radioactivity in cigarette smoke, a companion study (14) carried out in a room that had low ambient levels of radon showed that the radioactivity introduced directly into the air by the smoke could account for very little of the

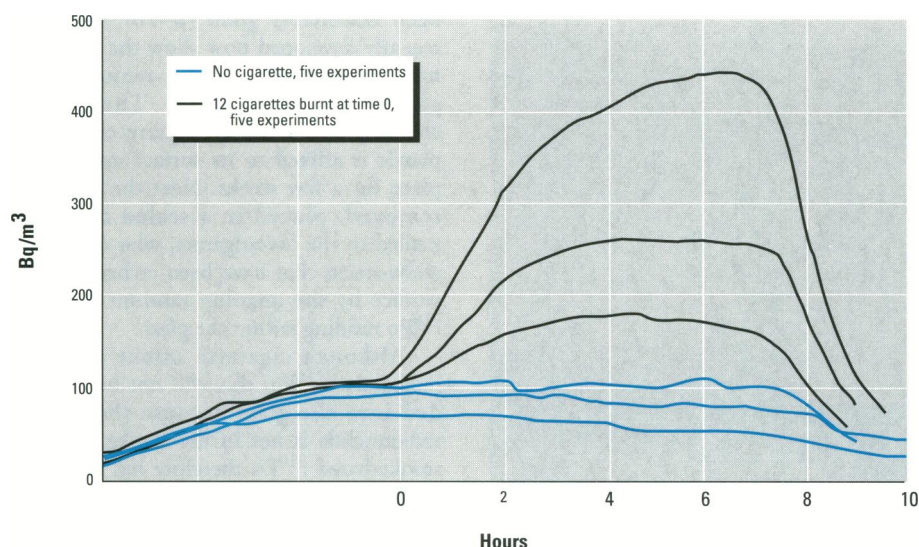


Figure 3. Data from Bergman et al. (14) showing the effect of cigarette smoke on the levels of airborne α radioactivity. Details given in text. (Reprinted with permission.)

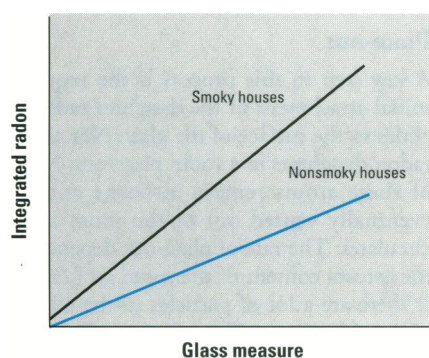


Figure 4. Schematic showing possible calibration curves relating the actual cumulative radon exposure to the glass-based result, leading to measurement confounding. An incremental change in the radon exposure has less effect on the glass in a smoky environment than in a nonsmoky environment, resulting in a steeper slope for smoky homes.

effect. Overall, these data suggest that smoke can serve as a carrier for radon-daughter radioactivity, and this effect can persist over many hours. To the extent that smoke can in this way reduce the rate of plate-out of radon daughters, the daughters are more likely to be vented out of the room rather than to attach to the surfaces of the room. This suggests that a given level of radon will contribute less embedded ^{210}Po to the glass of a smoky room than to the glass of a similar room with cleaner air.

The kind of phenomenon shown in Figure 3 has been recognized by laboratory researchers, who sometimes use tobacco smoke as an aerosol vector to enhance delivery of radon daughters to the lungs of experimental animals (15). In homes, the use of an air filtering device has been

shown to markedly reduce both the levels of airborne radon daughters and the estimated α -radiation dose to the lung (16).

The data of Mahaffey et al. (submitted) lend further support to the possibility that the fraction of the daughters that plate-out is reduced in a smoky environment. In a case-control study of Missouri women who were never- or ex-smokers, study subjects who had both long-term radon detector-based and glass-based measurements were categorized crudely according to their smoking habits after age 18 or according to the smoking habits of co-residents. Only the categories "light" and "moderate" contained enough subjects for comparative analysis. The incremental change in the α activity in the glass per unit change in the measured radon exposure was found to be less in homes with moderate smoking than in homes with light smoking. This is just what would be predicted from the Bergman data. Again, we see evidence that smoky environments retard the plate-out of radon daughters and reduce the amount of ^{210}Po embedded in the glass surfaces. Presumably, the same sort of distortions would occur with other types of air pollution as well, such as those typically present in smoggy city air.

The existence of such a phenomenon raises important biological questions about possible modification of the radon dose by smoke. The smoke could serve to increase the biologically effective radioactive dose to the lung by increasing the time α -emitting daughters remain airborne, although the actual effect of particulates on lung dose remains controversial and depends in complex ways on the distribution of particle sizes, which affects the "unattached" frac-

tion. Bergman et al. (14) proposed that the phenomenon they described could be the basis for the observed excess cancer risk associated with second-hand smoke, rather than a direct carcinogenic effect of the diluted smoke itself. In short, the presence of smoke may serve to make radon daughters more [or possibly less (17)] available to the lung, an effect that can be thought of as dose modification. These are clearly important questions, but beyond the scope of this paper.

Distinct Calibration Curves

Figure 4 shows the hypothesized relationships between ^{210}Po activity in glass and the mean exposure of the glass to radon. An incremental change in the exposure (radon) has a different effect on the glass in a smoky room than in a room with cleaner air. This can be thought of as differential calibration curves, where the proper curve relating the measurement to the exposure depends on the presence or absence of a risk factor for lung cancer, here cigarette smoke. Notice that this is not really a measurement error problem in the usual epidemiologic sense: both calibration curves can be considered "correct" and the problem remains.

What are the consequences of ignoring this difference in calibration curves and simply treating the ^{210}Po activity in the glass as a surrogate for long-term radon exposure? Clearly, if smoking is ignored, radon could spuriously appear to be protective, since smoky houses, where the lung cancer risk is elevated, will tend to show lower radon levels.

As a simple example, suppose the average plate-out is reduced by a factor of 0.75 in homes of smokers. [This is consistent, for example, with the data shown by Mahaffey et al. (submitted), although they only had sufficient data to compare houses with light and moderate smokers.] For simplicity, also suppose that smoking status is unrelated to true radon levels, and radon is unrelated to risk of lung cancer. If we consider the situation where each participant has lived in only one house and assume that 95% of cases and 35% of controls are smokers, then one can show [assuming the lognormal distribution of radon levels estimated by Nero (18)] that the unadjusted relative risk associated with the highest quintile of radon, relative to the aggregate of lower exposures, is 0.75. This spuriously indicates a strong protective effect.

More realistically, if smoking is "adjusted for" but the adjustment is incomplete, in other words, important smoking effects persist within each crudely defined smoking stratum, then the estimated effect of

radon will still be distorted toward showing no risk and may give evidence for protection, by the same kind of bias.

There is also a distortion affecting the assessment of combined effects of smoking and radon on lung cancer risk. Suppose there is a true model relating radon exposure to risk and suppose the true relationship is the same among smokers and nonsmokers. Regardless of the model, the incremental effect of a unit change in the glass measure will appear to be greater among smokers than among nonsmokers. Fundamentally this occurs because a unit change in smoky houses has a different meaning from the same unit change in houses with cleaner air. Fitting a noncontinuous model based on categorizing the exposure does not avoid the problem and will be prone to the same biases.

Choice of Exposure Method for Field Studies

Recent case-control studies have relied on long-term α -track etch detectors (3–5), usually left in place for a year to get an integrated measure over the seasons. Since this kind of device measures filtered radon, rather than the airborne daughters, the measurement should not be affected by the presence of smoke. So we can assume that the studies that have already been done are not subject to systematic biases in radon measurement related to smokiness.

On the other hand, problems of interpretation arise, even with track-etch measurements. Radon is not the active agent of interest: the exposure of interest is the short-lived daughters that irradiate the lung, radon itself being inert with a fairly long half-life. To the extent that the presence of smoke particles may decrease or increase the effective integrated dose to the respiratory tract, the traditional measurements based on radon gas may overestimate or underestimate the dose to the lung in smoky houses.

On the other hand, the traditional approaches do provide a robust measure of radon, and by including separate dosimetry for each former house, have the advantage that risk models can be fitted that allow for effects of time since exposure, provided one studies a residentially mobile population. By contrast, the glass-based approach is constrained by the historical weighting implied by Figure 2. Moreover, the method is subject to potential bias due to the presence of cigarette smoke.

Future of Glass-based Technology

The actual magnitude of the effect of smoke on glass-based measurement is difficult to predict on theoretical grounds, and

the bias described could be small enough to be overlooked in field studies of radon and lung cancer.

However, before retrospective assessment based on household glass can be used with confidence, more methodologic work is required. Health physicists need to carry out laboratory studies, measuring the plate-out of radon daughters onto glass, using controlled exposure chambers that can deliver a known amount of radon and smoke. More methodologic field studies of household glass should also be carried out. In particular, additional validation studies need to be done where measurements based on glass are compared with those based on radon in air, as measured by long-term track-etch detectors. The resulting regression slopes for smoky and nonsmoky houses should be compared, as in Figure 4.

Although the distortion of glass-based exposure assessment by the presence of smoke may ultimately lead to the conclusion that such methods should not be used for case-control studies of radon and lung cancer, the methods may ultimately be widely applicable for screening. Current EPA recommendations call for a short-term screening test to be done in the lowest living area of the house; if the result indicates a potential problem, a longer-term device is placed to get a more accurate measurement. At least several months of measurement are required to reduce errors due to day-to-day variations in radon levels. Using house-specific glass, such as the pane of a built-in cabinet or window in a house of known age, such a measurement could be accomplished with greater accuracy (9) and within a few weeks. Lively and Steck (9) also point out that the technique "has an advantage in that the embedded activity is tamper-proof." If screening is the goal, one would want to identify houses with potential levels exceeding some cut-off, currently established at 4 pCi/l by the EPA for the United States. For houses that are at least a few years old, one could use glass and a calibration curve appropriate to a smoky environment (the steeper line in Figure 4) to establish a conservative cut-point based on the α activity of appropriate window panes. Only houses that minimally exceed this cut-point would then require a follow-up long-term assessment.

In this way, most homeowners and buyers could be reassured fairly quickly that the house will not expose their families to excessive levels of radon. On the other hand, for houses with strong evidence of excess based on the glass measurements, remediation could be started right away. With this strategy, the houses with truly high levels could be targeted more effi-

ciently than under the current approaches. To accomplish this goal, the glass-based technology will, however, need to be developed further, validated, and made widely available.

Appendix

Calculation of the Curve Shown in Figure 2

The curve of Figure 2 shows the appropriate weighting function that determines the α activity in the glass due to its exposure at various times, following the simplifying assumption that the conditions of exposure of the glass (ventilation rates, temperature, air turbulence, etc.) have remained approximately constant over the lifetime of the glass. The exposure may not have remained constant, as, for example, when the piece of glass has been carried from house to house as the study subject changed residences.

Since radioactive decay is exponential, the curve is derived as a simple integral, as follows. Suppose we follow the fate of an incremental exposure due to the radon that was present in a room t years ago. The intermediate daughters with very short half-lives can be neglected, because virtually all of that radon will have decayed to ^{210}Pb within a few weeks. The fraction of these lead atoms that persists in the form of ^{210}Po can be calculated as an integral. If the ^{210}Pb decays according to $C[\exp(-t\lambda)]$ and ^{210}Po decays according to $C[\exp(-t\delta)]$, then we know that λ is $\ln(2)/22$ and δ is $\ln(2)/(138/365)$, if t is expressed in years. This follows from the knowledge of their respective half-lives as 22 years and 138 days. The events leading to ^{210}Po involve decay of ^{210}Pb at time s followed by the survival of ^{210}Po for time lasting at least $t - s$. Then we simply need to integrate over all choices of s from 0 to t , as follows:

$$\int_0^t \lambda e^{-\lambda s} e^{-\delta(t-s)} ds = \frac{\lambda}{(\delta - \lambda)} [e^{-\lambda t} - e^{-\delta t}]$$

This corresponds to the curve displayed in Figure 2. If a piece of glass has had a time-varying exposure, as in typical scenarios where people move from house to house, then the resulting activity in the glass should be approximately proportional to the integral of the product of the curve showing the true radon levels multiplied by the curve of Figure 2. The proportionality constant depends on the plate-out rate for radon daughters and the ventilation rates for the rooms in which the glass was exposed.

Of course, if the glass has been exposed in several different residences over its life-

time, the residual embedded α activity determined by the exposures and subsequent decays cannot distinguish between high exposures that happened long ago and moderate exposures of recent origin. Thus with this method of measurement, the integration described cannot be deconvolved, and consequently one cannot fit risk models that take into account effects of time since exposure.

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